IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:
Brian Sorrentino et al.

Application No.: 09/866,866 | Confirmation No.: 4688

Filed: May 29, 2001 | Art Unit: 1644

For: ANTIBODIES HAVING BINDING SPECIFICITY FOR THE EXTRACELLULAR DOMAIN OF A BREAST CANCER RESISTANCE PROTEIN (BCRP) (as amended) | Examiner: M. A. Belyavskyi

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Honorable Commissioner for Patents
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REPLY BRIEF

This Reply Brief is filed in response to the Examiner's Answer, mailed March 24, 2008, maintaining rejection of claims 16, 22-24, and 29-34.

This Reply Brief contains items under the following headings as required by 37 C.F.R. § 41.41 and M.P.E.P. § 1208:

(1) Real Party in Interest

(2) Related Appeals and Interferences

(3) Status of Claims

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(5) Summary of Claimed Subject Matter

(6) Grounds of Rejection to be Reviewed on Appeal

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Appendix A - Claims

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(1) Real Party in Interest

The real party in interest in the present Appeal is St. Jude Children's Research Hospital, the assignee, as evidenced by the assignment set forth at Reel 012121 Frame 0660.

(2) Related Appeals and Interferences

None

(3) Status of Claims

This application contains claims 16, 22-24, and 29-34, each of which were finally rejected in an Office Action mailed May 14, 2007. On August 14, 2007, Applicant appealed from the final rejection of claims 16, 22-24, and 29-34 (all claims currently under examination in this application).

(4) Status of Amendments

Applicant's Appeal Brief dated November 14, 2007 was considered by the Examiner prior to the filing of this Reply Brief. No amendments have been made since the Office Action mailed May 14, 2007.

(5) Summary of Claimed Subject Matter

This section is reproduced verbatim from the Appeal Brief filed on November 14, 2008 (Sect. 5 at pp. 2-3).

One aspect of Appellant's invention, as recited in independent claim 16, provides an isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16); wherein the extracellular portion of the BCRP is in its natural conformation (specification, page 9, lines 22-23); wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface (specification, page 39, line 5 - page 40, line 2); wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface (specification, page 23, lines 25-29; page 39, lines 19-22; page 22, line 26 -page 24, line 17); and wherein the antibody does not bind to denatured BCRP (specification, page 23, lines 13-26; page 22, line 26 - page 24, line 17).

Another aspect of Appellant's invention, as recited in independent claim 31, is an antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16) generated by three steps. These three steps are (i) immunizing an animal with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 9, lines 22-23; page 39, line 5 - page 40, line 2); (ii) selecting a hybridoma that secrets antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and do not bind to denatured BCRP (specification, page 23, lines 13-29; page 39, lines 19-22; page 22, line 26 - page 24, line 17); and (iii) isolating an antibody from the hybridoma selected in step (ii) (specification, page 39, line 30 - page 40, line 2).

In yet another aspect of Appellant's invention, as recited in independent claim 33, an isolated antibody is claimed. The antibody claimed in claim 33 binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16; page 9, lines 22-23) generated by isolating an antibody from a hybridoma that secretes antibodies that bind to MCF-7 cells (specification, page 39, line 17 - page 40, line 2) that express buBCRP or mBCRP in its natural conformation on the cell surface (specification, page 23, lines 25-29; page 39, lines 19-22), wherein said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 23, lines 25-29; page 39, lines 19-22); wherein said antibodies do not bind to denatured BCRP (specification, page 23, lines 13-16; page 22, line 26 - page 24, line 17); and wherein the hybridoma is generated from an animal immunized with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 39, line 13 - page 40, line 2).

(6) Grounds of Rejection to be Reviewed on Appeal

In the Office Action mailed May 14, 2007, claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 112, first paragraph "as containing subject matter which was not described in

the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." This basis for rejection was withdrawn by the Examiner in the Answer mailed March 24, 2008 (see Examiner's Answer at p. 3) and, consequently, is no longer under review.

The following grounds for rejection remain and are reviewed on this appeal:

I. claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 112, second paragraph as indefinite;

II. claims 16, 22, and 31-34 were rejected under 35 U.S.C. § 102(e) in view of U.S. Patent No. 6,313,277 ("the '277 patent");

III. claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 102(e) in view of U.S. Patent No. 6,485,933 ("the '933 patent");

IV. claims 16, 23, 24, and 29 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent in view of Owens *et al.*, *J. of Immunological Methods 168*: 149-165 (1994) ("Owens"); and

V. claims 16 and 30 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent or the '933 patent each in view of U.S. Patent No. 4,281,061 ("the '061 patent") in view of Owens.

(7) Argument

I. Patentability of Claims 16, 22-24, and 29-34 under 35 U.S.C. § 112, ¶ 2.

In rejecting claims 16, 22-24, and 29-34 under 35 U.S.C. § 112, ¶ 2, the Examiner originally argued that these claims were rendered indefinite by Applicant's failure to recite SEQ ID NOs not only for BCRP, but also for huBCRP and mBCRP. *See, e.g.*, Office Action mailed May 14, 2007, at 2 ("Claim 16, 22-24 and 29-34 are indefinite and ambiguous in the recitation of BCRP protein in the second line and huBCRP or mBCRP."). In the Answer to Applicant's Appeal Brief, however, the Examiner focuses solely on the lack of SEQ ID NOs for BCRP. *See* Examiner's Answer mailed March 24, 2008, at 4 ("Claim 16, 22-24 and 29-34 are indefinite and

ambiguous in the recitation of BCRP protein in the second line."). Thus, with respect to huBCRP and mBCRP, the Examiner concedes that recitation of SEQ ID NOs in the claims is not required where, as here, the specification defines BCRP on a species-specific basis and discloses corresponding SEQ ID NOs for each of the claimed species-specific BCRP protein.

Insofar as the Examiner acknowledges that recitation of "huBCRP" and "mBCRP," does not render the claims indefinite, Applicant respectfully submits that rejection of claims 16, 22-24, and 29-34 under 35 U.S.C. § 112, ¶ 2 should be entirely withdrawn. Independent claims 16, 31, and 33—from which the remaining claims depend—recite the Markush group: "[a]n isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) *selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP).*" Thus, because the claimed subject matter is limited to the species-specific BCRP recited within the Markush group (*i.e.*, huBCRP and mBCRP), no SEQ ID NOs need be recited to further define the term BCRP. The term BCRP is not indefinite because it clearly refers to species-specific BCRP that are defined in the specification and for which SEQ ID NOs are provided.

II. and III. Patentability Under 35 U.S.C. § 102(e)

Claims 16, 22, and 31-34 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6, 313,277 ("the '277 patent") and claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,485,933 ("the '933 patent").

Independent claim 16 is directed to isolated antibodies wherein the antibody *binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)* selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its *natural conformation*; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody *does not bind to denatured BCRP*.

Each of claims 22-24 and 29 depend from claim 16, and claim 30 specifically recites the antibody according to claim 16. Thus, the novelty of claims 22-24, 29, and 30 necessarily follows from the novelty of independent claim 16.

Independent claim 31 is directed to isolated antibodies that *bind to an extracellular portion of a BCRP* selected from the group consisting of huBCRP or mBCRP generated by:

(i) immunizing an animal with 3T3 cells that express huBCRP or mBCRP in its *natural conformation* on the cell surface;

(ii) selecting a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, wherein said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and *do not bind to denatured BCRP*; and

(iii) isolating an antibody from the hybridoma selected in step (ii).

Claim 32 depends from claim 31. Thus, the novelty of claim 32 necessarily follows from the novelty of independent claim 31.

Independent claim 33 is directed to isolated antibodies wherein the antibody *binds to an extracellular portion of a BCRP* selected from the group consisting of huBCRP or mBCRP; wherein the antibody is generated by isolating an antibody from a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its *natural conformation* on the cell surface; wherein said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface; wherein said antibodies *do not bind to denatured BCRP*; and wherein the hybridoma is generated from an animal immunized with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface.

Claim 34 depends from claim 33. Thus, the novelty of claim 34 necessarily follows from the novelty of independent claim 33.

* * *

The Examiner maintains that the '277 and '933 patents disclose isolated polyclonal and monoclonal antibodies that bind to BCRP (Examiner's Answer at pp. 4 and 10 referencing, *e.g.*, column 4, lines 50-60 of the '277 patent and Examiner's Answer at pp. 4 and 10, referencing, *e.g.*, Abstract and column 16, lines 15-30 of the '933 patent). The Examiner concedes that "the reference[s are] silent about the antibody binding to an extracellular portion of BCRP or does not bind to denatured BCRP" but alleges that "said functional limitation[s] would be inherent properties of the referenced antibody, because the referenced antibody was obtained against the same antigen as claimed" (emphasis added).

The Examiner further alleges that it is Applicant's burden to show that the reference antibodies do not bind to denatured BCRP as recited in the claims "[s]ince the office does not have a laboratory to test the reference antibodies." Examiner's Answer at pp. 4-5 and 10-11, citing *In re Best*, 195 U.S.P.Q. 430, 433 (CCPA 1977); *In re Marosi*, 218 U.S.P.Q. 289, 292-93 (Fed. Cir. 1983); *In re Fitzgerald*, 205 U.S.P.Q. 594 (CCPA 1980)).

With respect to claims 31-34, which are directed to methods for producing an antibody that binds to BCRP, the Examiner concedes that the method for producing "is different from the referenced monoclonal antibody that binds to BCRP," but alleges that "the instant claims are drawn to a product (antibody) and the patentability of the product does not depend on its method of production." Examiner's Answer at pp. 5 and 11, citing *In re Thrope*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985); MPEP § 2113 and *Noell v. Lederman*, 255 F.3d 1343 (Fed. Cir. 2004).

Each of the Examiner's bases for maintaining the rejection under 35 U.S.C. § 102(e) is addressed below.

A. The Examiner Has Not Met the Burden of Proving Inherent Anticipation by a Prophetic Disclosure of Antibodies Raised Against an Antigen that Is Distinct from the Antigen Used to Generate the Claimed Antibodies

The Examiner errs in alleging that, because the Patent Office does not have a laboratory to test the reference antibodies, Applicant bears the burden of proving that the reference antibodies do not possess the claimed functional attributes of (1) binding to an extracellular portion of BCRP and (2) not binding to denatured BCRP.

On the contrary, it is well established that the Examiner bears the burden of "provid[ing] a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 ¶ IV (emphasis added). Because the Examiner has not provided a basis in fact and/or technical reasoning why it necessarily flows from the teachings in the '277 or '933 patents that an antibody made against a *purified* BCRP protein would, *inter alia*, (1) bind to an extracellular portion of BCRP and (2) not bind to denatured BCRP, the Examiner has not met the burden of setting forth a *prima facie* case of inherent anticipation.

The Examiner's sole "technical reasoning" for asserting that antibodies made by the methods disclosed in the '277 and '933 patents inherently possess the claimed functional properties derives from an erroneous assertion that the prior art antibodies are generated against the "same antigen" as are the antibodies presented in the instant claims. This is plainly incorrect.

As described below, the antigen described in the '277 and '933 patents is a *purified* BCRP protein whereas the antigen disclosed in the application presently under appeal is BCRP *expressed on the surface of a 3T3 cell*. Thus, for the reasons discussed, *infra*, it does not "necessarily flow" from the disclosure of the '277 patent or the '933 patent that antibodies prophetically disclosed therein would inherently possess the claimed functional properties of (1) *binding to the extracellular domain of a BCRP* protein it its *natural conformation* and (2) *not binding to denatured BCRP*.

Because the Examiner has not set forth any reasoning why it would follow from the '277 patent disclosure or the '933 patent disclosure that antibodies directed against a purified BCRP protein would *necessarily* bind to the extracellular domain of BCRP in its natural conformation and not to denatured BCRP, the Examiner has failed to make a *prima facie* showing that the prior art antibodies inherently possessed the claimed functional properties. Thus, the Examiner has not met his burden of "provid[ing] a basis in fact and/or technical reasoning" supporting the inherent anticipation of any of the instant claims.

B. The Antigen Employed by Applicant to Achieve the Claimed Antibodies is not the Antigen Described in Either the '277 Patent or '933 Patent

The Examiner errs in alleging that the antigen used by Applicant to generate the claimed antibodies is the same as the antigen described in the '277 and '933 patents. *See* Examiner's Answer at p. 10 (noting with respect to the '277 patent that "the referenced antibody was obtained against the same antigen, i.e. not denatured BCRP, as claimed in the instant claims") and at p. 13 (noting the same with respect to the '933 patent). Contrary to the Examiner's position, however, the antigen used by Applicant to generate the claimed antigen is, in fact, quite distinct from the antigen described in the '277 and '933 patents.

The instant disclosure teaches the generation of antibodies by immunizing an animal with 3T3 cells expressing BCRP. *See, e.g.*, application page 23, lines 1-16 and page 39, lines 1-12. Expression of BCRP within a cellular context allows the protein to assume its *natural conformation* within the cell membrane such that the protein's extracellular domain is physically separate from its membrane spanning and cytoplasmic domains. Thus, the only portion of BCRP available to the immune system of an animal in which antibodies are raised against this 3T3-BCRP antigen is the BCRP extracellular domain. Furthermore, and as described in the Sarkadi Declaration at ¶ 5 and the Sarkadi Supplemental Declaration at ¶ 5, BCRP normally forms a homodimer when expressed on the surface of a cell. Thus, the antigen used in the instant specification is a whole 3T3 cell presenting antigenic epitopes from the *extracellular domain of BCRP in its natural conformation*. Moreover, because the antigen is presented in its natural conformation, antibodies raised against BCRP expressed on the surface of a cell *do not specifically bind to denatured BCRP*.

By contrast, the '277 patent describes the generation of antibodies by immunizing animals with "a preparation of BCRP," Col. 4, lines 50-52, which is generated by the purification of BCRP. *See* Sarkadi Declaration ¶ 5. Similarly, the '933 patent states that "purified BCRP may be used to produce antibodies." Col. 18, lines 54-55. Thus, the antigen disclosed in the '277 patent and '933 patent is purified BCRP protein. As noted by Dr. Sarkadi, "[s]uch a purified protein would not be expected to adopt the three-dimensional structure of BCRP as it is found in the cell membrane." Sarkadi Supplemental Declaration ¶ 5.

Thus, the purified BCRP disclosed in the '277 patent and the '933 patent is not the same antigen as BCRP expressed on the surface of a cell; only the latter is in its natural conformation with its extracellular domain exposed and its transmembrane and cytoplasmic domains shielded from an animal's immune system.

Disparity in epitope presentation is likely to be particularly striking where the native protein, like BCRP, resides in the cell membrane and dimerizes; in such cases, the protein's natural conformation is intimately dependent on interaction both with the cell membrane lipids and with the binding partner(s). Consequently, and as noted by Dr. Sarkadi, "any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." Sarkadi Declaration ¶ 5.

Moreover, given that the antibodies taught by the '277 and '933 patents are raised against denatured BCRP protein, any such antibodies will also, of necessity, bind to denatured BCRP protein. Contrast this with the antibodies taught by the instant specification; although, prior to selection and purification, some of these antibodies may recognize epitopes shared by denatured BCRP and the extracellular domain of BCRP in its natural conformation, many will recognize epitopes possessed only by the latter.

Because purified BCRP protein, separated from a cellular membrane, cannot adopt a natural conformation, antibodies raised against purified BCRP protein will possess binding specificities that are distinct from antibodies raised against BCRP expressed on the surface of a cell. For example, antibodies raised against purified BCRP may bind to the protein's transmembrane, cytoplasmic, or extracellular domains, while antibodies raised against BCRP expressed on the surface of a cell will bind exclusively to the protein's extracellular domain. Any antibodies raised against purified BCRP that bind to the protein's extracellular domain will bind to BCRP that is <u>not</u> in its natural conformation while antibodies raised against BCRP expressed on the surface of a cell will bind to the protein's extracellular domain that has adopted its natural conformation such as, for example, through BCRP homodimerization. More importantly, because purified BCRP is removed from its native environment within a cell membrane, the protein becomes denatured during the purification process. Antibodies raised

against purified BCRP will, thus, bind to denatured BCRP while antibodies raised against BCRP expressed on the surface of a cell will bind to BCRP in its natural conformation.

While a purified BCRP protein and a BCRP protein expressed on the surface of a cell may, hypothetically, share one or more epitopes, these two distinct antigens will each possess many unique epitopes. Thus, antibodies raised against a purified BCRP protein will not necessarily, and indeed likely will not, exhibit the claimed functional attributes of *binding to the extracellular domain of a BCRP protein* in its *natural conformation* and *not binding to a denatured BCRP protein*.

Finally, the Examiner errs in relying on statements made in the '277 patent that antibodies raised against a purified BCRP protein "can be administered to patient to reduced (sic) resistance to chemotherapy drugs" (Examiner's Answer at pp. 11-12) and in the '933 patent that such antibodies can be used for "detecting and measuring the expression of BCRP, for example in FACS assay" (Examiner's Answer at pp. 12-13). Such gratuitous statements do not support the Examiner's position that antibodies raised against a purified BCRP protein would inherently bind to the extracellular domain of a BCRP protein in its natural conformation. Furthermore, such statements in no way provide evidence that such antibodies would not bind to a denatured BCRP protein as expressly recited in the instant claims.

IV. and V. Patentability Under 35 U.S.C. § 103(a)

Claims 16, 23, 24, and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent in view of Owens *et al.*, *J. Immunol. Methods* 168:149-165 (1994) ("Owens") and claims 16 and 30 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent or the '933 patent each in view of U.S. Patent No. 4,281,061 ("the '061 patent).

Independent claim 16 is directed to isolated antibodies wherein the antibody *binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)* selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its *natural conformation*; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living

MCF-7 cells that do not express BCRP on their surface; and wherein the antibody *does not bind to denatured BCRP*.

Each of claims 23, 24, and 29 depend from claim 16, and claim 30 specifically recites the antibody according to claim 16. Thus, the non-obviousness of claims 23, 24, 29, and 30 necessarily follows from the non-obviousness of independent claim 16.

The Examiner cites the '277 and '933 patents for the teachings described herein, *supra*. The Examiner concedes that the '277 patent fails to teach an isolated chimeric antibody, as recited in claim 23; an isolated humanized antibody, as recited in claim 24; or an isolated antibody attached to a detectable label, as recited in claim 29. The Examiner concedes that neither the '277 patent nor the '933 patent teaches a kit comprising in a suitable container an antibody that binds to BCRP.

The Examiner cites Owens for teaching, *inter alia*, chimeric and humanized antibodies and attaching antibodies to a detectable label. Thus, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to produce chimeric or humanized monoclonal antibody based on, or to attach a detectable label to, the antibodies taught by the '277 patent.

The Examiner cites the '061 patent for teaching that "reagents of the pharmaceutical compositions can be provided as kits as a matter of convenience, optimization and economy of the users" (Examiner's Answer at p. 8, citing to the '061 patent at col. 22, line 62 through col. 23, line 4). Thus, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to apply the teachings of the '061 patent to those of the '933 or '277 patents to obtain a claimed kit comprising the antibody that binds to BCRP.

Because neither Owens nor the '061 patent remedy any of the deficiencies noted, *supra*, in the '277 or '933 patents, instant claims 16, 23, 24, 29, and 30 are necessarily non-obvious over the '277 or '933 patents in view of the teachings of Owens and the '016 patent. More specifically, because neither Owens nor the '061 patent teach or suggest antibodies that *bind to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)* in its *natural conformation* and that *do not bind to denatured BCRP*, instant claims 16, 23, 24, 29, and 30 are non-obvious over the '277 or '933 patents in view of the teachings of Owens and the '016 patent.

(8) Claims

A copy of the claims involved in the present appeal is attached hereto as Appendix A. These claims are identical to those finally rejected in an Office Action mailed May 14, 2007 and presented in the Appeal Brief filed on November 14, 2007.

(9) Evidence

The following documents were presented in Appendix B of the Appeal Brief filed on November 14, 2007: (a) Sarkadi Declaration - OIPE date stamped October 28, 2003 and (b) Sarkadi Supplemental Declaration - OIPE date stamped February 22, 2005.

(10) Related Proceedings

No related proceedings are ongoing as indicated in (2) above.

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Respectfully submitted,

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APPENDIX A

Claims under appeal:

16. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its natural conformation; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP.

22. The isolated antibody of claim 16 wherein the isolated antibody is monoclonal.

23. The isolated antibody of claim 16 wherein the isolated antibody is chimeric.

24. The isolated antibody of claim 23 wherein the antibody is humanized.

29. The isolated antibody of claim 16, operably attached to a detectable label.

30. An immunodetection kit comprising, in suitable container means, the antibody according to claim 16 and an immunodetection reagent.

31. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) generated by

(i) immunizing an animal with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface;

(ii) selecting a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and do not bind to denatured BCRP; and

(iii) isolating an antibody from the hybridoma selected in step (ii).

32. The antibody of claim 31, which is generated in a mouse and wherein the BCRP is human BCRP.

33. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) generated by isolating an antibody from a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and said antibodies do not bind to denatured BCRP, and wherein the hybridoma is generated from an animal immunized with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface.

34. The antibody of claim 33, wherein the animal is a mouse and the BCRP is human BCRP.

APPENDIX B – EVIDENCE

The following documents were presented in Appendix B of the Appeal Brief filed on November 14, 2007:

Sarkadi Declaration - OIPE date stamped October 28, 2003

Sarkadi Supplemental Declaration - OIPE date stamped February 22, 2005

APPENDIX C – RELATED PROCEEDINGS

None.